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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/286,166	04/05/1999	DANA M. FOWLKES	CPI-012CP4BC	4623

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LAHIVE & COCKFIELD
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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/286,166	Fowlkes, DM et al.
Examiner	**Art Unit**
Michael Brannock	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 2, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *43-60* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *43-60* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 25, 2/3/03, and those of Applicant's supplemental response of 4/4/03 (Paper 27) have been entered in full.

2. Claims 43-58 and new claims 59 and 60 are pending.

Response to Amendment

3. It is noted that Applicant intends to submit a request for interference under 37 C.F.R. § 1.607 with U.S. Patent No: 5691188.

4. At page 3 of Paper 27, Applicant asserts that the original and newly added claims are fully supported by the written description of the specification and claims of the originally filed parent application, 08/041,431. In particular, applicant alleges that support for heterologous and non-yeast GPCRs is found in the specification and claims of the parent application. As discussed below regarding the new rejection under 35 U.S.C. 112, second paragraph, it is not clear what is encompassed by the term "non-yeast" receptor. If Applicant intends that the term limit the claims to heterologous GPCRs that do not include a coding sequence from a yeast gene, then there does not appear to be adequate written description of such in the parent Application. To the contrary, the specification discusses the art-recognized need to include yeast coding sequences

into the heterologous GPCR so that the heterologous GPCR will insert correctly into the yeast cell membrane and couple to downstream effectors (e.g. pg 15, L14-15). As discussed previously, both King et al (Science 250(121-123)1990) and the Sledziewski patent (5284746) teach that heterologous mammalian G-protein coupled receptors can be made to work in the claimed assay systems if those receptors contain various portions of the yeast receptor. However, the specification merely suggests that "it is conceivable that a foreign receptor which is expressed in yeast will functionally integrate into the yeast membrane and therefore interact with the endogenous yeast G-protein. More likely, either the receptor will need to be modified (e.g. by replacing its V-VI loop with that of the yeast STE2 or STE3 receptor), or a compatible G-protein should be provided" see page 16, first paragraph of the 08/041,431 application.

Thus, the 08/041,431 application appears to acknowledge the art-recognized difficulty encountered when attempting to use the invention with a native mammalian receptor that lacks yeast sequences and only provides the speculation that GPCRs can be found that do not require yeast sequences. The skilled artisan understands that the mere assertion that "it is conceivable" that these GPCRs might be found, does not put Applicant is in possession of such a genus of GPCRs. Simply verbalizing that it is "conceivable" that the GPCRs might be found does not place Applicant in possession of the GPCRs. In fact, no working examples of mammalian GPCRs, with or without yeast sequences (other than the recited prior art), were provided in the 08/041,431 application. The specification simply provides a list of references indicating which

mammalian receptors had been cloned. Nor are any such working examples provided in the subsequent Application, 08/190328, filed approximately 8 months later.

The Declaration of Dr. Broach, under 35 USC §1.132, is acknowledged. However, the Declaration appears to relate to the instant application, and not to the 08/041,431 application. It is noted that there are no rejections under 35 U.S.C. 112, first paragraph, applicable to the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New claim 60 requires "non-yeast" receptors. While parent application 080410431 uses this term in claims 17-23, there does not appear to be any definition of this term in the specification, yet the skilled artisan would expect that the term encompassed all receptors that are not found in yeast, i.e. heterologous receptors, including those receptors that contain portions of yeast receptors (hybrid receptors) but are not normally found in yeast. The term clearly refers to the whole receptor, i.e. it does not stipulate that a receptor should have no portions in common with a yeast receptor, only that it be a non-yeast receptor; and thus would encompass anything

not normally found in a yeast. However, at page 3 of paper 27, Applicant contends that the intended meaning of the phrase excludes hybrid receptors. This argument has been fully considered but not deemed persuasive. The specification has not set forth what is intended to be encompassed by the phrase, and given its broadest reasonable interpretation, the phrase includes hybrid receptors, i.e. those not normally found in yeast.

Double Patenting

5. Claims 43-58 stand and new claims 59 and 60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 6100042, as set forth in item 6 of Paper 9. It is acknowledged that Applicant intends to address the propriety of the this rejection upon an indication that the application is otherwise in condition for allowance.

6. Applicant is advised that should claim 43 be found allowable, claim 60 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

7. Claims 43, 44, 45, 47, 50, 51, 52, 54, 55, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5284746 (to Sledziewski et al.) and King et al. Science 250(121-123)1990 in view of Kang, YS. et al. Mol. Cell. Biol. 10(2582-2590)1990.

U.S. Patent No. 5284746 discloses a transformed yeast cell comprising a reporter gene (see col 12, L43, e.g. LacZ see col 12, L65-66) under the control of a pheromone-responsive promoter (see col 12, L42; e.g. FUS1 promoter see col 12, L48-56), a heterologous mammalian G-protein coupled receptor gene (β2- adrenergic receptor, for example, see col 1), wherein said receptor is a hybrid receptor comprising intracellular sequences from yeast and sequences from heterologous receptors (see col 3, L2), wherein said yeast receptor sequences are STE2 sequences (see col 4, L33), wherein said receptor is capable of inducing yeast pheromone response (see col 4, L5), each gene being under the control of a separate promoter (second construct) (see col 12, L 41), and a mutation in the ste2 gene causing increased sensitivity to receptor activation (see col 10, L8-9).

King et al. disclose an assay similar to that discussed above, yet instead of mutating the intracellular sequences of the mammalian GPCR such that they interact with the endogenous yeast G-protein, as taught by Sledziewski, King et al. teach that the endogenous Gα-protein can be replaced with a heterologous mammalian Gαs (see the Abstract). King et al., also teach that the N-terminal extracellular portion of the mammalian receptor should be replaced with the

equivalent portion of the yeast STE2 protein to facilitate expression of the GPCR into the membrane of the yeast cell, see col 2 of page 121. King et al. also teach that it is the Gα subunit of the G-protein that determines the specificity of the receptor/G-protein interaction, as is well appreciated in the art, see col 1 of page 121. Although Sledziewski et al. teach a hybrid G-protein coupled receptor and King et al. teach a heterologous G-protein, neither Sledziewski nor King et al. teach the use of a heterologous hybrid G-protein in the assay.

Kang et al. present another, more attractive, option that would not require mutation of the intracellular portions of the mammalian GPCR, as taught by Sledziewski et al. and would allow for the use of Gα subunits other than the mammalian Gαs taught by King et al. King et al. had reasoned that because mammalian Gαs can function in yeast to compliment the growth arrest phenotype of yeast cells lacking the endogenous Gα, then this property could be utilized at the basis of the functional assay, e.g. to couple the mammalian GPCR to the pheromone responsive pathway, see col. 3 of page 121. Kang et al. also teach that mammalian Gαs can compliment the growth arrest phenotype of yeast cells lacking the endogenous Gα, but Kang et al. teach that mammalian Gαi does so very poorly, and that Gαo does not do so at all, see Table II. Strikingly, Kang demonstrate that chimeric Gα subunits comprising the N-terminal of the yeast Gα subunit fused to the mammalian Gαs, Gαi, or Gαo subunit can complement the growth arrest phenotype, see Table II.

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to use hybrid Gα proteins instead of hybrid G-

protein receptors in the assay disclosed in U.S. Patent No. 5284746 or mammalian Gαs, as taught by King. The motivation to do would arise from the fact that it would have been obvious to one of ordinary skill in the art that it is desirous to mutate as little as possible the GPCR which is the subject of study, and by Kang et al. who stated that portions of mammalian Gα proteins (Gαi) which bind to mammalian receptors but do not interact with yeast βγ subunits could be made to do so by expressing them as hybrid proteins containing yeast sequences (See col 2 of page 2588 and table 2).

Applicant's argues that Sledziewski's solution to the problem of getting heterologous GPCRs to interact productively with yeast cells was to construct hybrid receptors not hybrid G-proteins, e.g. by changing intracellular sequences of the mammalian receptor and replacing them with yeast sequences. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art would appreciate that *had* Sledziewski et al. known of the work of Kang et al. at the time of filing, Sledziewski would certainly have been motivated to leave the intracellular sequences of the mammalian receptors intact and instead produce hybrid G-proteins as taught by Kang et al. The purpose of the assay taught by Sledziewski is to screen for ligands of the mammalian receptor, e.g. col 2, 33-39; thus the artisan of ordinary skill would be desirous to keep to a minimum the differences between the sequence of the native receptor and that of the receptor used in the assay, particularly in view of the well recognized importance of the intracellular loops (referred to as effector domains, col 7, beginning at line 12) in determining the physical properties of the receptor, e.g. mediating receptor phosphorylation, desensitization, etc.

col 7, beginning at line 12). One of ordinary skill in the art practicing the invention of Sledziewski, upon learning from Kang et al., that portions of mammalian Gα proteins (Gαs, Gαi or Gαo which bind to mammalian receptors but do not interact with yeast βγ subunits could be made to do so by expressing them as hybrid proteins containing yeast sequences (See col 2 of page 2588 and table 2) would certainly be motivated to make changes in the G-protein and not in the receptor if it is the receptor that is the subject of investigation, as is taught by Sledziewski.

Applicant arguments relating to King et al. are not persuasive. King et al. use the rat Gαs subunit to transduce the signal from the heterologous receptor to the yeast Gβγ subunits. The rat Gαs subunit is known to interact with the particular mammalian receptor used by King et al. and also with the endogenous yeast Gβγ subunits. Thus, in this example, there would be no need to use a hybrid Gαs subunit, unless of course, a hybrid receptor was found to work more efficiently in the assay. Never-the-less, the instant invention encompasses the use of mammalian receptors that do not effectively interact with the rat Gαs subunit, e.g. those that interact with mammalian Gαi or Gαo . Mammalian Gαi or Gαo do not interact effectively with the endogenous yeast Gβγ subunits (e.g. see Table II of Kang). Kang et al. teach that the mammalian Gαi and Gαo subunits, which bind to mammalian receptors but do not interact effectively with yeast βγ subunits, can be made to couple to the yeast Gβγ subunits by expressing the Gαi or Gαo as a hybrid protein containing yeast sequences (See col 2 of page 2588 and table 2).

Applicant's points out, several times (page 6), that the hybrid Gα proteins of Kang et al. do not interact with the yeast receptor. Applicant urges that Kang teach that heterologous or

hybrid Gα proteins cannot interact with the yeast receptor. Yet it is simply unclear what point Applicant is trying to make. The artisan practicing the invention of Sledziewski or King is interested in mammalian receptors, not in the yeast receptors. In fact, Sledziewski teach that a preferred embodiment is to mutate the gene for the yeast receptor such that the yeast receptor is not produced (see col 10, L8-9). As set forth previously, The Kang N-terminal hybrid Gα subunits and wild-type rat Gαs subunit have the same properties with regard to the complementation of growth arrest phenotype (i.e. they all bind to yeast Gβγ), yet they do not bind to the yeast receptor (i.e. do not allow mating). Thus, the rat Gαs subunit and the hybrid Gαs, Gαi and Gαo subunits have the same activities with respect to yeast receptor binding and with respect of the interaction with the yeast Gβγ. Although neither the rat Gαs subunit nor the hybrid subunits bind to yeast receptors, it is known, of course, that the rat Gαs subunit does bind to mammalian receptors, thus one of ordinary skill in the art would look to the Kang hybrid Gαs, Gαi and Gαo subunits to be used in conjunction with their cognate mammalian receptors.

Applicant cites *In re Herschler*, that no motivation to substitute ingredients set forth in a primary reference where referenced example was already complete. This argument has been fully considered but not deemed persuasive. As discussed above, an artisan of ordinary skill in the art would appreciate that it would be better than not to avoid changing amino acids in the effector domain of a receptor if is the receptor that is the object of study. The use of hybrid Gα subunits, as taught by Kang, provide a desirous alternative, i.e. it would be desirous to fit the G-

protein to the receptor if the purpose was to find biologically relevant compounds that bind to and activate or inhibit the receptor, as taught by Sledziewski.

Applicant argues that the examiner's use of the phrase "would not be dissuaded" from using hybrid Gα subunits does not meet the test of obvious. This argument has been fully considered but not deemed persuasive. The examiner used this phrase in response to Applicant's assertion that the teachings of Kang teach away from using the hybrid Gα subunits in the method of Sledziewski. The examiner indicated that not only would an artisan not be dissuaded, "but to the contrary", i.e. the artisan would be *motivated* to use the hybrid Gα subunits. At page 2588, col 2, 1st full paragraph, Kang et al. state: "These results indicate sufficient conservation of structure between yeast and mammalian Gα proteins to allow the function of appropriate domains in the hybrids and suggest that, like [rat] Gαs and Gαi, these hybrid proteins can interact with Gβγ but not with the pheromone receptors". Thus, Kang et al. provide both the suggestion and expectation of success to make a hybrid Gα subunit with the binding properties of rat Gα proteins.

8. Claims 46, 48, 49, 53, 55 and 56 stand rejected and new claims 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5284746 and Kang, YS. et al. Mol. Cell. Biol. 10(2582-2590)1990 for the reasons put forth above regarding claims 43, 44, 45, 47, 50, 51 52, 54, 55, 57 and 58 and in further view of Chang et al.. (Cell 63:999-1011,1990), as

set forth in item 9 of Paper 9. Applicant's arguments regarding U.S. Patent No. 5284746 and Kang et al. have been addressed above.

Conclusion

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

June 12, 2003

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